UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/638,210	08/07/2003	Dongxiao Zhang	EPIT-001	5792

24353 7590 03/14/2007
BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/638,210	ZHANG ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/11/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1/9/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed 12/11/06 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 1-13), and species of the method steps of molecular modeling an antibody from a VH1-a1 allotype rabbit to identify surface exposed amino acid residues, comparing the rabbit antibody framework sequence to human antibody framework sequences to identify the most similar human antibody, and substituting surface exposed amino acid residues in the rabbit antibody with corresponding amino acid residues in the human antibody, where the substitutions are not in the D-E loop region in Applicant's said response filed 6/26/06.

Claims 1 and 3-13 read on the elected species.

Applicant is reminded that upon consideration of the prior art, the search had been extended to include the species recited in instant claim 2.

Accordingly, claims 14-20 (non-elected groups II-IV) stand withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-13 are presently being examined.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the limitation "said nucleic acid sequence" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim.

5. For the purpose of prior art rejections, the filing date of the instant claim 3 is deemed to be the filing date of the instant application, *i.e.,* 8/7/03, as the parent provisional application serial no. 60/404,117 does not support the claimed limitation "further comprising identifying amino acids in a D-E loop region of said parent antibody and substituting only those amino acids that are not in said D-E loop."

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claim 3 is rejected under 35 U.S.C. 102(e) as being anticipated by US 20050048578 A1 (priority to 6/26/03, of record).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

US 20050048578 A1 discloses a method of making a humanized rabbit monoclonal antibody that is less immunogenic in a human, said method comprising resurfacing a rabbit monoclonal antibody (mAb), including a VH1-a1 allotype, by surface alignment comparison, *i.e.,* by comparing the amino acid sequences of the heavy and light chain variable regions with the most homologous human germline antibody genes, then predicting the surface residues in FR1, FR2 and FR3 of the most homologous human antibodies, identifying the rabbit framework residues at homologous positions, and substituting framework amino acid residues that are exposed in the rabbit mAb with the corresponding framework amino acid residues from the human antibody.
US 20050048578 A1 discloses that the framework regions have high homology to human sequences, and that the finding that rabbit antibody sequences can be readily aligned with human sequences shows that rabbit antibodies may be altered without substantially changing the conformation of rabbit antibody molecules, and thus retain the affinities of the modified rabbit antibodies. US 20050048578 A1 discloses changing Cys 80 in a parent mAb to the amino acid residue (Phe) found at position 80 of the human antibody. US 20050048578 A1 discloses making the humanized rabbit antibodies without substantially changing the conformation of the antibodies and further discloses use of the CAMEL modeling method to predict backbone conformations of all six CDRs and well as FR regions, and the interchain contact residues are expected to be non-surface exposed amino acid residues. US 20050048578 A1 discloses that it is preferable to produce an antibody that specifically binds to its corresponding antigen with a binding affinity of 10^{-8} M or more. US 20050048578 A1 exemplifies identifying amino acid residues of the framework region of the parent antibody that are not proximal to a CDR and substituting only those amino acid residues that are not proximal to said CDR, and teaches the importance of certain framework residues proximal to

CDRs in maintaining the conformation of the CDRs and the affinity of the antibody, and identifying those residues located close to CDRs that may need to be preserved as rabbit residues in the humanized antibodies (especially [0059], [0016], [0148]-[0155], Figures 3 and 5, claim 3).

With regard to the inclusion of claim 3 in this rejection, although the art reference does not explicitly disclose identifying amino acid residues in a D-E loop region of the parent antibody and substituting only those amino acid residues that are not in the D-E loop, the D-E loop amino acid residues do not appear to be part of the framework amino acid residues, nor the CDR residues, and the art method teaches retention of the rabbit CDR residues while changing surface exposed framework residues. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference).

Spieker-Polet *et al* teach that rabbit monoclonal antibodies are more useful than murine monoclonal antibodies because rabbits recognize antigens and epitopes that are not immunogenic in mice or rats and because rabbit antibodies are of high affinity. Spieker-Polet *et al* teach making monoclonal antibodies to human melanoma antigens. Spieker-Polet *et al* teach that rabbit monoclonal antibodies will be useful in diagnosis of diseases and treatment of patients (especially abstract, introduction and last paragraph of article).

Spieker-Polet *et al* do not teach wherein the rabbit monoclonal antibody is resurfaced, as recited in the instant claims.

Morea *et al* teach resurfacing by comparing the sequences of the variable domains of a non-human antibody with human variable domains, and substituting the surface framework residues of the non-human antibody with the corresponding human residues. Morea *et al* teach maintaining antigen specificity and affinity of the non-human antibody that is resurfaced. Morea *et al* teach that key-site surface residues should not be changed, nor should antigen binding contact sites, nor should any residues be changed that alter the structure of the antigen binding site. Morea *et al* teach that all key residues necessary to maintain the conformation of the hypervariable loops (*i.e.,* the CDRs) should be maintained. Morea *et al* teach that the advantage of resurfacing procedure over CDR grafting is that the design of the humanized antibody is much simpler and that, as only surface residues are mutated, the core of the non-human antibody variable domain is unchanged and consequently it is more likely that both the antigen binding loop conformations and their relative position in the resurfaced antibody are similar to those of the starting antibody. Morea *et al* teach molecular modeling of the variable domains, including the framework regions using as a template the domain of known structure with the highest sequence identity with the target domain. Morea *et al* teach that the residues adjacent to the loop should be taken into account when modeling, particularly the four residues before the N-terminus of the loop and the four residues after its C-terminus are used to superimpose structures. Morea *et al* teach maintaining the antigen specificity and binding affinity of the non-human antibody by not changing key-site specific residues (see entire article especially page 276 at column 2 starting at the first full paragraph and continuing through the first full paragraph on page 277, and page 272 at column 1 through page 274 at the first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have resurfaced a rabbit monoclonal antibody taught by Spieker-Polet *et al* using the resurfacing method taught by Morea *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to prepare a less immunogenic monoclonal antibody for use in humans as taught by Morea *et al* because Spieker-Polet *et al* teach that rabbit monoclonal antibodies will be useful for treatment of patients, *i.e.,* for treatment of humans.

With regard to the inclusion of claim 3 in this rejection, although the art reference Morea *et al* does not explicitly teach identifying amino acid residues in a D-E loop region of the parent antibody and substituting only those amino acid residues that are not in the D-E loop, the D-E loop amino acid residues do not appear to be part of the framework amino acid residues, nor the CDR residues, and the art method teaches retention of the rabbit CDR residues while changing surface exposed framework residues. With regard to the inclusion of claim 2 in this rejection, although the art reference Morea *et al* does not explicitly teach substituting residues that are not proximal to the CDR, the art reference teaches that four residues N-terminal as well as C-terminal to the CDR should be considered important in

modeling, so appears that these proximal residues are not be substituted. Therefore, the claimed process appears to be similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

10. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference) as applied to claims 1-9 above and further in view of Harlow and Lane (Antibodies, A Laboratory Manual, 1988, pages 27-29) and Mountain and Adair (Biotechn. Genet. Eng. Rev. 1992, 10: 1-142).

The combination of Spieker-Polet *et al* and Morea *et al* has been discussed supra.

The combined references do not teach wherein the resurfaced antibody has a binding affinity of 10^8 M^{-1} or greater for a specific antigen.

Harlow and Lane teach the required affinities of antibodies for several common immunochemical techniques begin at 10^8 M^{-1}, and that antibodies of that affinity produce strong binding (especially Table 3.1 on page 28).

Mountain and Adair teach that it is very likely that for most therapeutic applications, monoclonal antibodies with minimum dissociation constants of 10^{-9} to 10^{-10} M will be essential to achieve efficacy and to permit economically realistic doses (especially page 8 at the second full paragraph and the paragraph spanning pages 112-113).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a resurfaced antibody per the teaching of the combined references with high affinity of 10^8 M^{-1} or 10^9 M^{-1} taught by Harlow and Lane, or 10^{-9} to 10^{-10} M taught by Mountain and Adair (*i.e*, 10^9 M^{-1} or 10^{10} M^{-1}).

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a humanized monoclonal rabbit antibody as per the teaching of the combined references with the affinities taught by Harlow and Lane and by Mountain and Adair necessary for strong binding in a variety of immunochemical techniques in order to use the antibody per the teaching of Spieker-Polet *et al* in diagnosis as well as for therapy as taught by Mountain and Adair.

11. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference) as applied to claims 1-9 above, and further in view of Su *et al* (PNAS USA 1999, 96: 9710-9715) and Freedman *et al* (Immunochemistry, 1975, 12(4): 263-272).

The combination of Spieker-Polet *et al* and Morea *et al* has been discussed supra.

The combined references do not teach wherein the rabbit antibody is from a rabbit of known VH allotype, nor wherein the rabbit antibody is from a rabbit homozygous for a VH allotype, including wherein the allotype is VH1-a1, VH1-a2 or VH1-a3.
Su *et al* teach that the VH1 is preferentially used in VDJ rearrangement, and about 80% of the rabbit serum Ig molecules are composed of the product of this gene, which group has three allotypes, a1, a2 and a2 encoded by three alleles at the VH1 locus, VH1-a1, Vh1-a2 and Vh1-a3, respectively (abstract and introduction).

Freedman *et al* teach antibodies from light chain allotype defined pedigreed rabbits.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have taken the rabbit antibody from a rabbit of known VH allotype, including one homozygous for one of the VH1 allotypes taught by Su *et al* and optionally including homozygosity for one of the light chain allotypes taught by Freedman *et al* for resurfacing as per the teaching of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to restrict the allotype of the antibodies taught by the method of Spieker-Polet *et al* for simplifying molecular modeling taught by Morea *et al* and because allotype defined rabbits is taught by Freedman *et al*. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because monoclonal antibody production in mice and rats is accomplished using inbred strains of mice and rats with defined allotypes.

12. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference) as applied to claims 1-9 above, and further in view of Su *et al* (PNAS USA 1999, 96: 9710-9715) and McCormack *et al* (J. Immunol. 1988, 141(6): 2063-2071).

The combination of Spieker-Polet *et al* and Morea *et al* has been discussed supra.

The combined references do not teach wherein the rabbit antibody is from a rabbit of known VH allotype, nor wherein the rabbit antibody is from a rabbit homozygous for a VH allotype, including wherein the allotype is VH1-a1, VH1-a2 or VH1-a3.

Su *et al* teach that the VH1 is preferentially used in VDJ rearrangement, and about 80% of the rabbit serum Ig molecules are composed of the product of this gene, which group has three allotypes, a1, a2 and a2 encoded by three alleles at the VH1 locus, VH1-a1, Vh1-a2 and Vh1-a3, respectively (abstract and introduction).

McCormack *et al* teach that the H chain variable region (VH) of rabbit Ig molecules can be readily characterized on the basis of a series of serologically defined allotypes, and each rabbit expresses one large VH subgroup or family designated VHa, which encompasses 70 to 90% of the serum Ig molecules, the remaining 10% to 30% of the molecules being distributed among several minor serologically defined VH subgroups collectively referred to as VHa-negative. McCormack *et al* teach that amino acid sequence data reveal a remarkable degree of divergence between the VHa allotypes, sequences of the VH FR^4 differ by 7% to 15%. McCormack *et al* teach that fifteen amino acid residues within FR1 and FR3 are associated with one or another of the three VHa allotypes. McCormack *et al* teach residues at four additional positions, as well as an addition/deletion of a residue at position 2, distinguish the VHa-negative sequences from the VHa sequences, and thus the allotype-associated residues appear to be located on the surface of the V domain and therefore are in a position to contribute to the multiple serologic determinants or allotopes shown to comprise each allotype. McCormack *et al* teach rabbits homozygous for one allotype (especially introduction section on page 2063).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have taken the rabbit antibody from a rabbit of known VH allotype, including one homozygous for one of the VH1 allotypes taught by Su *et al* and McCormack *et al* to resurface per the teaching of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to restrict the allotype of the antibodies taught by the method of Spieker-Polet *et al* for simplifying molecular modeling taught by Morea *et al* and because allotype defined rabbits is taught by McCormack *et al* and the predominant VHa allotypes are taught by both McCormack *et al* and by Su *et al*. In addition, one of

ordinary skill in the art at the time the invention was made would have been motivated to do this because monoclonal antibody production in mice and rats is accomplished using inbred strains of mice and rats with defined allotypes.

13. Claims 1-10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rader *et al* (Biol. Chem. 2000, 275(18): 13668-13676, IDS reference) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference).

Rader *et al* teach that the rabbit antibody repertoire is a novel and attractive source for the generation of therapeutic human antibodies. Rader *et al* further teach humanized rabbit anti-human A33 antibodies produced by CDR grafting and framework fine tuning. Rader *et al* teach that the resulting humanized antibodies were found to retain both high specificity and affinity for the human A33 antigen (especially abstract). Rader *et al* teach that the highest affinity antibody had an affinity of 1.7 nM, comparable to that of the parental rabbit clone, *i.e.,* having a binding affinity greater than 10^8M^{-1} (paragraph spanning columns 1 and 2 on page 13673 and last paragraph of article on page 13675). Rader *et al* teach that nonhuman antibodies are highly immunogenic in humans thereby limiting their potential use for therapeutic applications, especially when repeated administration is necessary. Rader *et al* teach that the growing significance of antibody-based strategies for the treatment of a variety of diseases demands efficient and reliable routes to human or humanized antibodies with high specificity and affinity (first paragraph of article on page 13668). Rader *et al* teach *in vitro* assessment of the humanized antibodies but do not teach that the humanized antibodies were tested *in vivo* for immunogenicity.

Rader *et al* does not teach wherein the rabbit antibodies are resurfaced, as recited in the instant claims.

Morea *et al* teach resurfacing by comparing the sequences of the variable domains of a non-human antibody with human variable domains, and substituting the surface framework residues of the non-human antibody with the corresponding human residues. Morea *et al* teach maintaining antigen specificity and affinity of the non-human antibody that is resurfaced. Morea *et al* teach that key-site surface residues should not be changed, nor should antigen binding contact sites, nor should any residues be changed that alter the structure of the antigen binding site. Morea *et al* teach that the advantage of resurfacing procedure over CDR grafting is that the design of the humanized antibody is much simpler and that, as only surface residues are mutated, the core of the non-human antibody variable domain is unchanged and consequently it is more likely that both the antigen binding loop conformations and their relative position in the resurfaced antibody are similar to those of the starting antibody. Morea *et al* teach molecular modeling of the variable domains, including the framework regions using as a template the domain of known structure with the highest sequence identity with the target domain (see entire article especially page 276 at column 2 starting at the first full paragraph and

continuing through the first full paragraph on page 277, and page 272 at column 1 through page 274 at the first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used in the method of humanizing a non-human antibody by resurfacing as taught by Morea *et al* to humanize the rabbit monoclonal antibodies taught by Rader *et al,* including ones of other specificity than to the A33 antigen.

One of ordinary skill in the art at the time the invention was made would have resurfaced the rabbit monoclonal antibodies taught by Rader *et al,* including ones of other specificity than to the A33 antigen, because Morea *et al* teach that the advantage of resurfacing procedure over CDR grafting is that the design of the humanized antibody is much simpler and as only surface residues are mutated, the core of the non-human antibody variable domain is unchanged; consequently it is more likely that both the antigen binding loop conformations and their relative position in the resurfaced antibody are similar to those of the starting antibody. In addition, one of ordinary skill in the art at the time the invention was made would have done this in order to compare the immunogenicity of the humanized antibodies produced by each method *in vivo* for each antibody specificity.

With regard to the inclusion of claim 3 in this rejection, although the art reference does not explicitly disclose identifying amino acid residues in a D-E loop region of the parent antibody and substituting only those amino acid residues that are not in the D-E loop, the D-E loop amino acid residues do not appear to be part of the framework amino acid residues, nor the CDR residues, and the art method teaches retention of the rabbit CDR residues while changing surface exposed framework residues. With regard to the inclusion of claim 2 in this rejection, although the art reference Morea *et al* does not explicitly teach substituting residues that are not proximal to the CDR, the art reference teaches that four residues N-terminal as well as C-terminal to the CDR should be considered important in modeling, so appears that these proximal residues are not be substituted. Therefore, the claimed process appears to be similar to the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

14. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rader *et al* (Biol. Chem. 2000, 275(18): 13668-13676, IDS reference) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference) as applied to claims 1-10 and 13 above, and further in view of Su *et al* (PNAS USA 1999, 96: 9710-9715) and McCormack *et al* (J. Immunol. 1988, 141(6): 2063-2071).

The combination of Rader *et al* and Morea *et al* has been discussed supra.

The combined references do not teach wherein the rabbit antibody is from a rabbit of known VH allotype, nor wherein the rabbit antibody is from a rabbit homozygous for a VH allotype, including wherein the allotype is VH1-a1, VH1-a2 or VH1-a3.

Su *et al* teach that the VH1 is preferentially used in VDJ rearrangement, and about 80% of the rabbit serum Ig molecules are composed of the product of this gene, which group has three allotypes, a1, a2 and a2 encoded by three alleles at the VH1 locus, VH1-a1, Vh1-a2 and Vh1-a3, respectively (abstract and introduction).

McCormack *et al* teach that the H chain variable region (VH) of rabbit Ig molecules can be readily characterized on the basis of a series of serologically defined allotypes, and each rabbit expresses one large VH subgroup or family designated VHa, which encompasses 70 to 90% of the serum Ig molecules, the remaining 10% to 30% of the molecules being distributed among several minor serologically defined VH subgroups collectively referred to as VHa-negative. McCormack *et al* teach that amino acid sequence data reveal a remarkable degree of divergence between the VHa allotypes, sequences of the VH FR^4 differ by 7% to 15%. McCormack *et al* teach that fifteen amino acid residues within FR1 and FR3 are associated with one or another of the three VHa allotypes. McCormack *et al* teach residues at four additional positions, as well as an addition/deletion of a residue at position 2, distinguish the VHa-negative sequences from the VHa sequences, and thus the allotype-associated residues appear to be located on the surface of the V domain and therefore are in a position to contribute to the multiple serologic determinants or allotopes shown to comprise each allotype. McCormack *et al* teach rabbits homozygous for one allotype (especially introduction section on page 2063).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have taken the rabbit antibody from a rabbit of known VH allotype, including one homozygous for one of the VH1 allotypes taught by Su *et al* and McCormack *et al,* to resurface per the teaching of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to restrict the allotype of the antibodies taught by the method of Rader *et al* for simplifying molecular modeling taught by Morea *et al* and because allotype defined rabbits is taught by McCormack *et al* and the predominant VHa allotypes are taught by both McCormack *et al* and by Su *et al.* In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because monoclonal antibody production in mice and rats is accomplished using inbred strains of mice and rats with defined allotypes.

15. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of US Patent No. 5,369,641.

Spieker-Polet *et al* teach that rabbit monoclonal antibodies are more useful than murine monoclonal antibodies because rabbits recognize antigens and epitopes that are not immunogenic in mice or rats and because rabbit antibodies are of high affinity. Spieker-Polet *et al* teach making monoclonal antibodies to human melanoma antigens. Spieker-Polet *et al* teach that rabbit monoclonal antibodies will be useful in diagnosis of diseases and treatment of patients (especially abstract, introduction and last paragraph of article).

Spieker-Polet *et al* do not teach wherein the rabbit monoclonal antibody is resurfaced, as recited in the instant claims.

US Patent No. 5,369,641 discloses resurfacing rodent antibodies that have improved therapeutic efficacy due to the presentation of a human surface in the variable region. US Patent No. 5,369,641 discloses that the method of resurfacing includes position alignments of a pool of antibody heavy and light chain variable regions to give a set of heavy and light chain variable region framework surface exposed positions wherein the alignment positions for all variable regions are at least about 98% identical, a set of heavy and light chain variable region framework surface exposed amino acid residues is defined for the nonhuman antibody or fragment thereof by molecular modeling, a set of heavy and light chain variable region framework surface exposed amino acid residues that is most closely identical to the set of nonhuman surface exposed amino acid residues is identified, and said set is substituted with the set of heavy and light chain variable region framework surface exposed amino acid residues identified except for those amino acid residues that are within 5 Angstroms of any atom of any CDR residue, *i.e.,* except those that are proximal to a CDR, and producing the humanized antibody having the binding specificity of the parent nonhumanized antibody (see entire reference, especially abstract, summary of the invention and claims).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have humanized the rabbit monoclonal antibodies taught by Spieker-Polet *et al* using the resurfacing method disclosed by US Patent No. 5,369,641.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Spieker-Polet *et al* teach that rabbit antibodies are more useful than murine antibodies, are of high affinity and are useful for diagnosis and therapy, and US Patent No. 5,369,641 teaches human anti-non-human antibody responses are deleterious and a method for humanizing non-human antibodies in order to minimize these responses.

With regard to the inclusion of claim 3 in this rejection, although the art reference Morea *et al* does not explicitly teach identifying amino acid residues in a D-E loop region of the parent antibody and substituting only those amino acid residues that are not in the D-E loop, the D-E loop amino acid residues do not appear to be part of the framework amino acid residues, nor the CDR residues, and the art method teaches retention of the rabbit CDR residues while changing surface exposed framework residues. Therefore, the claimed process appears to be similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

16. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of US Patent No. 5,369,641 as applied to claims 1-9 above, and further in view of Su *et al* (PNAS USA 1999, 96: 9710-9715) and McCormack *et al* (J. Immunol. 1988, 141(6): 2063-2071).

The combination of Spieker-Polet *et al* and US Patent No. 5,369,641 has been discussed supra.

The combined references do not teach wherein the rabbit antibody is from a rabbit of known VH allotype, nor wherein the rabbit antibody is from a rabbit homozygous for a VH allotype, including wherein the allotype is VH1-a1, VH1-a2 or VH1-a3.

Su *et al* teach that the VH1 is preferentially used in VDJ rearrangement, and about 80% of the rabbit serum Ig molecules are composed of the product of this gene, which group has three allotypes, a1, a2 and a2 encoded by three alleles at the VH1 locus, VH1-a1, Vh1-a2 and Vh1-a3, respectively (abstract and introduction).
McCormack *et al* teach that the H chain variable region (VH) of rabbit Ig molecules can be readily characterized on the basis of a series of serologically defined allotypes, and each rabbit expresses one large VH subgroup or family designated VHa, which

encompasses 70 to 90% of the serum Ig molecules, the remaining 10% to 30% of the molecules being distributed among several minor serologically defined VH subgroups collectively referred to as VHa-negative. McCormack *et al* teach that amino acid sequence data reveal a remarkable degree of divergence between the VHa allotypes, sequences of the VH FR^4 differ by 7% to 15%. McCormack *et al* teach that fifteen amino acid residues within FR1 and FR3 are associated with one or another of the three VHa allotypes. McCormack *et al* teach residues at four additional positions, as well as an addition/deletion of a residue at position 2, distinguish the VHa-negative sequences from the VHa sequences, and thus the allotype-associated residues appear to be located on the surface of the V domain and therefore are in a position to contribute to the multiple serologic determinants or allotopes shown to comprise each allotype. McCormack *et al* teach rabbits homozygous for one allotype (especially introduction section on page 2063).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have taken the rabbit antibody from a rabbit of known VH allotype, including one homozygous for one of the VH1 allotypes taught by Su *et al* and McCormack *et al* to resurface, per the teaching of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to restrict the allotype of the antibodies produced by the method of the combined references for simplifying molecular modeling taught by Morea *et al,* and because allotype defined rabbits is taught by McCormack *et al,* and the predominant VHa allotypes are taught by both McCormack *et al* and by Su *et al*. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because monoclonal antibody production in mice and rats is accomplished using inbred strains of mice and rats.

17. Claims 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spieker-Polet *et al* (PNAS USA 1995, 92: 9348-9352) in view of US Patent No. 5,369,641 as applied to claims 1-9 above, and further in view of Harlow and Lane (Antibodies, A Laboratory Manual, 1988, pages 27-29) and Mountain and Adair (Biotechn. Genet. Eng. Rev. 1992, 10: 1-142).

The combination of Spieker-Polet *et al* and US Patent No. 5,369,641 has been discussed supra.

The combined references do not teach wherein the resurfaced antibody has a binding affinity of 10^8 M^{-1} or greater for a specific antigen.

Harlow and Lane teach the required affinities of antibodies for several common immunochemical techniques begin at 10^8 M^{-1} and greater (especially Table 3.1 on page 28).

Mountain and Adair teach that it is very likely that for most therapeutic applications, monoclonal antibodies with minimum dissociation constants of 10^{-9} to 10^{-10} M will be essential to achieve efficacy and to permit economically realistic doses (especially page 8 at the second full paragraph and the paragraph spanning pages 112-113).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a resurfaced antibody per the teaching of the combined references with high affinity of 10^{8} M^{-1} or 10^{9} M^{-1} taught by Harlow and Lane, or 10^{-9} to 10^{-10} M taught by Mountain and Adair (*i.e,* 10^{9} M^{-1} or 10^{10} M^{-1}).

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a humanized monoclonal rabbit antibody as per the teaching of the combined references with the affinities taught by Harlow and Lane and by Mountain and Adair necessary for strong binding in a variety of immunochemical techniques in order to use the antibody per the teaching of Spieker-Polet *et al* in diagnosis as well as for therapy as taught by Mountain and Adair.

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 7 of copending Application No. 10/637,317 in view of US Patent No. 5,369,641, Morea *et al* (Methods 20: 267-279, 2000, IDS reference), Su *et al* (PNAS USA 1999, 96: 9710-9715) and McCormack *et al* (J. Immunol. 1988, 141(6): 2063-2071). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The claims of '317 do not teach substituting only those framework amino acid residues that are not proximal to a CDR, nor substituting only those amino acid residues that are not in the D-E loop, nor wherein the identifying step involves molecular modeling of the parent or non-human antibody, nor wherein the amino acid residues substituted are at least two discontiguous amino acid residues, nor wherein the rabbit antibody is from a rabbit homozygous for a VH allotype recited in instant claim12, nor wherein the binding affinity of the resurfaced antibody is that recited in instant claim 13.

US Patent No. 5,369,641 discloses resurfacing rodent antibodies that have improved therapeutic efficacy due to the presentation of a human surface in the variable region. US Patent No. 5,369,641 discloses that the method of resurfacing includes position alignments of a pool of antibody heavy and light chain variable regions to give a set of heavy and light chain variable region framework surface exposed positions wherein the alignment positions for all variable regions are at least about 98% identical, a set of heavy and light chain variable region framework surface exposed amino acid residues is defined for the nonhuman antibody or fragment thereof by molecular modeling, a set of heavy and light chain variable region framework surface exposed amino acid residues that is most closely identical to the set of nonhuman surface exposed amino acid residues is identified, and said set is substituted with the set of heavy and light chain variable region framework surface exposed amino acid residues identified except for those amino acid residues that are within 5 Angstroms of any atom of any CDR residue, *i.e.,* except those that are proximal to a CDR, and producing the humanized antibody having the binding specificity of the parent nonhumanized antibody (see entire reference, especially abstract, summary of the invention and claims).

Morea *et al* teach resurfacing by comparing the sequences of the variable domains of a non-human antibody with human variable domains, and substituting the surface framework residues of the non-human antibody with the corresponding human residues. Morea *et al* teach maintaining antigen specificity and affinity of the non-human antibody that is resurfaced. Morea *et al* teach that key-site surface residues should not be changed, nor should antigen binding contact sites, nor should any residues be changed that alter the structure of the antigen binding site. Morea *et al* teach that the advantage of resurfacing procedure over CDR grafting is that the design of the humanized antibody is much simpler and that, as only surface residues are mutated, the core of the non-human antibody variable domain is unchanged and consequently it is more likely that both the antigen binding loop conformations and their relative position in the resurfaced

antibody are similar to those of the starting antibody. Morea *et al* teach molecular modeling of the variable domains, including the framework regions using as a template the domain of known structure with the highest sequence identity with the target domain (see entire article especially page 276 at column 2 starting at the first full paragraph and continuing through the first full paragraph on page 277, and page 272 at column 1 through page 274 at the first full paragraph).

Su *et al* teach that the VH1 is preferentially used in VDJ rearrangement, and about 80% of the rabbit serum Ig molecules are composed of the product of this gene, which group has three allotypes, a1, a2 and a2 encoded by three alleles at the VH1 locus, VH1-a1, Vh1-a2 and Vh1-a3, respectively (abstract and introduction).

McCormack *et al* teach that the H chain variable region (VH) of rabbit Ig molecules can be readily characterized on the basis of a series of serologically defined allotypes, and each rabbit expresses one large VH subgroup or family designated VHa, which encompasses 70 to 90% of the serum Ig molecules, the remaining 10% to 30% of the molecules being distributed among several minor serologically defined VH subgroups collectively referred to as VHa-negative. McCormack *et al* teach that amino acid sequence data reveal a remarkable degree of divergence between the VHa allotypes, sequences of the VH FR^4 differ by 7% to 15%. McCormack *et al* teach that fifteen amino acid residues within FR1 and FR3 are associated with one or another of the three VHa allotypes. McCormack *et al* teach residues at four additional positions, as well as an addition/deletion of a residue at position 2, distinguish the VHa-negative sequences from the VHa sequences, and thus the allotype-associated residues appear to be located on the surface of the V domain and therefore are in a position to contribute to the multiple serologic determinants or allotopes shown to comprise each allotype. McCormack *et al* teach rabbits homozygous for one allotype (especially introduction section on page 2063).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of the claims of '317: to have substituted only those framework amino acid residues not proximal to a CDR as disclosed by US Patent No. 5,369,641 and to have used molecular modeling as disclosed by US Patent No. 5,369,641 and Morel *et al*, to have made the humanized antibody with an affinity disclosed by US Patent No. 5,369,641 that meets the limitation recited in instant claim 13, and to have used a rabbit antibody from a rabbit homozygous for the VH1-a1, 2 or 3 allotype taught by Su *et al* and McCormack *et al* in order to compare a rabbit antibody with a light chain paired with a heavy chain of known allotypic specificity.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a humanized rabbit monoclonal antibody of high affinity and specificity as taught by the art references.

Claims 5 and 7 of '317 recite changing framework amino acid residues that include surface exposed amino acid residues.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1-13 are directed to an invention not patentably distinct from claims 1-5 and 7 of commonly assigned 10/637,317 as enunciated supra.

21. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/637,317, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
March 21, 2007

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600